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(71) Applicant: COLOR ACCESS, INC. [US/US]; 7 Corporate Center Drive, Melville, NY 11747 (US).

(72) Inventors: MAES, Daniel, H.; 279A Nassau Road, Huntington, NY 11743 (US). MARENUS, Kenneth, D.; 62 McCulloch Drive, Dix Hills, NY 11746 (US). FTHENAKIS, Christina, G.; 9 Lucille Lane, Dix Hills, NY 11746 (US).

(74) Agent: TSEVDOS, Estelle, J.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

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(54) Title: CHOLESTEROL SULFATE COMPOSITIONS FOR ENHANCEMENT OF STRATUM CORNEUM FUNCTION

(57) Abstract

The present invention provides a method of retarding desquamation of the stratum corneum, and maintaining stratum corneum thickness, by applying to the skin an effective amount of cholesterol sulfate. The retardation of desquamation can be useful in enhancing the skin's own UV protection, in prolonging the retention time of a sunless tan, and generally reducing the appearance of lines and wrinkles associated with both photo- and chronoaging.

reducing the efficacy of this physical barrier and permitting easier penetration of harmful stimuli such as UV rays. This in turn leads to UV-damage to the dermal layers of the skin, resulting in degradation of collagen and elastin, finally resulting in wrinkling and skin atrophy. Moreover, the thinning of the stratum corneum can result in a greater visibility of the wrinkling and atrophy, the cause of which is rooted in the dermis.

Notwithstanding the obvious importance of the stratum corneum in maintaining a healthy youthful appearance of the skin, rehabilitation and maintenance of the dermis has been a major cosmetic focus in preventing the appearance of aging; relatively little attention has been paid to developing cosmetic means for maintaining a fairly consistent level of stratum corneum function into old age. The present invention now provides a means for retaining this function, and concurrent uses relating to same.

Summary of the Invention

The invention relates to a method of increasing the thickness and cohesion of the stratum corneum of the skin, which comprises applying to skin an effective amount of cholesterol sulfate. The invention also relates to a method of protecting the skin against UV radiation comprising applying to the skin an effective amount of cholesterol sulfate. In another embodiment, application of cholesterol sulfate to the skin reduces desquamation, and therefore, skin flakiness. In yet another embodiment, the invention provides a method for enhancing a sunless tan which comprises applying a self-tanning agent, such as DHA in combination with an effective amount of cholesterol sulfate.

Brief Description of the Figures

Figure 1 illustrates the condition of stratum corneum thickness under different cholesterol sulfate treatment regimens, as described in Example I: (A)control (no treatment);(B)1% ethanol vehicle control; (C)cholesterol sulfate, 0.01µg/ml; (D)cholesterol sulfate, .1µg/ml; (E)cholesterol sulfate, 1µg/ml; (F)cholesterol sulfate 10µg/ml.

Figure 2 illustrates the duration of the self-tanning action of DHA with and without cholesterol sulfate.

Figure 3 illustrates the duration of the self-tanning action of DHA with and without cholesterol sulfate and a lipid mix.

Detailed Description of the Invention

The present invention, in its various embodiments, is predicated on the observation that cholesterol sulfate, when applied topically to the skin, enhances the cohesion of the stratum corneum resulting in a more prolonged retention of the layers of the stratum corneum. Specifically, it has been observed that application of cholesterol sulfate to skin cells results in a distinct, dose-dependent, increase in the thickness of the layers of the stratum corneum, as shown in Figures 1C-F. The observation is important for a number of different applications; a particularly significant application is in the maintenance of the texture of older skin. A current common means of enhancing smoothness of the skin is to encourage exfoliation. However, exfoliation necessarily involves a high rate of turnover of the stratum corneum, and consequent thinning of this layer of the skin. While not an issue in youthful skin, desquamation in older skin can, in some cases, simply exacerbate a problem already established, namely, the natural thinning observed with age. Thus, application of cholesterol sulfate to retard desquamation and maintain stratum corneum thickness represents an entirely new direction in the treatment and maintenance of older, thinning skin. A thicker stratum corneum aids in preventing or retarding the appearance of fine lines and wrinkles which so frequently characterize thinning skin. At the same time, the enhanced cohesion of the stratum corneum results in an effective strengthening of the protective lipid barrier naturally provided therein.

To achieve this effect, the cholesterol sulfate or salts thereof can be applied in any type of cosmetically or pharmaceutically acceptable vehicle for topical application with which the active component is compatible, e.g., a gel, a cream, a lotion, an ointment, a mousse, a spray, a solid stick, a powder, a

suspension, a dispersion, and the like. Preferably, however, the cholesterol sulfate is not provided in a liposome formulation, and is formulated in a composition containing relatively low levels of emulsifiers. Techniques for formulation of various types of vehicles are well known to those skilled in the art, and can be found, for example, in Chemistry and Technology of the Cosmetics and Toiletries Industry, Williams and Schmitt, eds., Blackie Academic and Professional, Second Edition, 1996, and Remington's Pharmaceutical Sciences, 18th Edition, 1990, the contents of which are incorporated herein by reference. Cholesterol sulfate is effective in the claimed function when provided in the composition in an amount of from about 0.05 to about 10%, preferably from about 0.5 to about 5%, most preferably about 1 to about 3%, all by weight of the total composition.

The thickening and cohesion of the stratum corneum also provides other benefits, which, in certain specific applications, can be appreciated by individuals of all ages. The stratum corneum represents an important physical barrier between the environment and the deeper skin layers as well as the internal organs. The presence of this thicker layer thus will provide a greater level of protection than is possible with a loose, flaking stratum corneum. Although this property can be exploited in a number of ways, perhaps the most important is the enhanced self-protection from UV rays. The thicker stratum corneum means an increase in the Minimal Erythemal Dose of UV which will result in sunburn or more serious skin damage. In connection with this aspect of the invention, cholesterol sulfate may be beneficially combined with one or more sunscreens for an enhanced UV protective composition which provides both short- and long-term protection. Thus, the invention provides sunscreen compositions comprising effective amounts of cholesterol sulfate and one or more sunscreens. Examples of useful sunscreens include, but are not limited to, inorganic sunscreens such as titanium dioxide, zinc oxide, and iron oxide; and organic sunscreens, such as camphor derivatives, cinnamates, salicylates, benzophenones, triazines, PABA derivatives, diphenylacrylate derivatives, and dibenzoylmethane derivatives. In such sunscreen compositions, cholesterol sulfate

is present in the amounts described above, and the respective sunscreens are present in the amounts normally used for UV protection.

An additional use of the cholesterol sulfate is in the enhancement and prolongation of self-tanning products. One of the recognized limitations of self-tanners, which are normally based on dihydroxyacetone(DHA) as the active component, is that the tan on the skin lasts only as long as the skin cells receiving the DHA remain in place. In the normal course of events, then, a self-applied tan usually lasts no more than 5 days, i.e., for as long as it takes for the stratum corneum layer to which the DHA was applied to fully turn over. When cholesterol sulfate is combined with DHA, or any other self-tanning agent, in a typical self-tanning formulation, however, the rate of turnover of the stratum corneum to which the composition is applied is slowed down, thereby permitting a longer rate of retention of the "tanned" cells, and thus prolonging the length of time the tan remains visible on the skin. Thus, the invention provides a self-tanning composition comprising an effective amount of cholesterol sulfate and an effective amount of a self-tanning agent. In a preferred embodiment, the self-tanner is DHA, which is usually applied in an amount of from about 2.5 to about 10% by weight of the formulation. The self-tanner may also be imidazole, preferably in combination with DHA, in an amount of about 1-10%, preferably about 1.5-7.5%.

In addition to its use in therapeutic products, cholesterol sulfate can also be beneficially added to color cosmetic products. In this regard, effective amounts of cholesterol sulfate are added to makeup formulations such as foundations, blushes, lipsticks and glosses, eyeliners, eyeshadows, and the like. A particular advantage may be obtained with such formulations, in that the retardation of desquamation may enhance makeup retention on the skin to which it is applied. The sunscreen/cholesterol sulfate combination may also be effectively employed in such products.

In all formulations in which cholesterol sulfate is employed, it is preferred that the cholesterol sulfate be combined

with other components of the naturally occurring lipid barrier. In a particularly preferred embodiment, the cholesterol sulfate is combined with at least one of each of fatty acids, ceramides, and a sterol, preferably cholesterol. Fatty acids may be up to 24 carbon atoms in length. Examples of preferred fatty acids include butyric acid, caproic acid, octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid, palmitic acid, stearic acid, linoleic acid and oleic acid. Particularly preferred are fatty acids with a C_{12} to C_{20} chain length.

The ceramides to be employed in the compositions of the invention are sphingolipids, having a sphingosine or related molecule backbone with fatty acids or ω-esterified fatty acids linked to an amino group on the sphingosine, and in some cases, with saccharide moieties linked to the terminal hydroxyl of the sphingosine. In particular, the compositions may contain ω-esterified ceramides or acylceramides, cerebrosides, ω-esterified cerebrosides, or acylglycosyl sphingolipids. Particularly preferred types of ceramides for the present compositions are ceramide III and cerebrosides.

In those compositions in which cholesterol sulfate is combined with these lipids, the lipid components each can be used in an amount of from about 0.05 to 10%, preferably 0.5 to about 5%, most preferably about 1 to about 3%, all by weight of the total composition. In a particularly preferred embodiment, the cholesterol sulfate and the lipid components are present in substantially equal amounts in the composition. It will be understood from the foregoing that the lipid component need not be pure lipid, but rather may be natural extracts containing one or more desirable lipids, and used in amounts consistent with attaining the concentrations recommended above.

The compositions of the invention are applied to the skin in a manner appropriate to the intended end result. For example, for the general promotion of the appearance of young, healthy skin by retardation of desquamation and maintenance of stratum corneum, the the best results are achieved after regular application over a period of time. A preferred method of obtaining the benefits of the composition is via chronic topical application of a safe and

effective amount of a composition containing cholesterol sulfate. It is suggested as an example that topical application of the composition, in an amount of from about 0.1 mg/cm² to 2 mg/cm² of skin, be performed from about once per week to about 4 or 5 times daily, preferably from about 3 times a week to about 3 times daily, most preferably about once or twice per day. By "chronic" application, it is meant herein that the period of topical application may be over the lifetime of the user, preferably for a period of at least about one month, more preferably from about three months to about twenty years, more preferably from about six months to about ten years, more preferably still from about one year to about five years, thereby resulting in the treatment or prevention of the external signs of photo- or chronoaging.

When the composition is used in conjunction with a sunscreen, it is applied in the same amounts as specified above, on an as-needed basis, to mitigate the effects of exposure to the sun. When used in combination with a self-tanner, the composition is also applied in similar amounts, on the portion of the skin to be tanned, with repetition, again, on an as-needed basis.

The invention is further illustrated by the following non-limiting examples:

Example I

This example illustrates the ability of cholesterol sulfate to retard desquamation and maintain stratum corneum thickness.

Matek skin equivalents are obtained and prepared for use in accordance with the supplier's protocol. Equilibrated skins are treated topically with dilutions of cholesterol sulfate. Cholesterol sulfate is solubilized 1 mg/ml in ethanol, and serially diluted 10-fold to yield doses of 0.01, .1, 1 and 10µg/ml. Each dose is added topically to an equivalent, using a 100µl volume. Treatment is repeated daily along with media replacement over a three day period. One sample is treated with 1% ethanol, representing a vehicle control. Following treatment, equivalents are fixed according to standard protocol, and sent for histological preparations. Figures 1A-F show stained sections of the two controls plus the treatment samples. The figures show a

very loose organization of the stratum corneum in the media control, with a gradual increase in organization and cohesion of the stratum corneum seen in the treatment samples, which increases with the amount of cholesterol sulfate in the treatment. Some compaction is seen in the ethanol treated sample, which is believed due to dehydration of the sample combined with lipid removal.

Example II

The following is a composition according to the present invention:

Material	Weight %
Phase I	
isocetyl alcohol	2.5
octyl hydroxystearate	2.0
alpha hydroxylauric acid	0.5
Phase II	
purified water	QS
cyclodextrin	1.0
Phase III	
ethoxydiglycol	5.0
laureth-23	1.5
dipropylene glycol	1.0
sodium hyaluronate(1%)	1.2
pantethine	0.1
PhaseIV	
sucrose	2.0
dihydroxyacetone	5.0
Phase V	
cyclomethicone	12.0
dimethicone	3.0
cyclomethicone/dimethicone	2.0
tricaprylyl citrate	1.5

dimethicone	3.0
Phase VI	
malvaceae extract	0.2
fragrance	0.4
tocopheryl acetate	0.1
wheat bran extract	0.2
linoleic acid	0.2
sodium cholesterol sulfate	0.2
Phase VII	
nylon-12	2.0
Phase VIII	
polyquaternium-37/propylene glycol	1.2

Example III

A study is conducted to determine the effect of cholesterol sulfate on skin flakiness, as an indicator of its effect in reducing desquamation. Fifteen subjects between the ages of 21 and 65 years are selected for the study. The subjects report for the study without moisturizers or any other products on their hands and their baseline measurements are taken. The subjects are given a product containing 0.5% cholesterol sulfate in a water and oil emulsion base to take home and self-administer on their right hands only, twice a day in the morning after washing and in the evening at least 15 minutes before bedtime for four weeks. The left hand serves as the untreated control site. The subjects are only allowed to use the test product and specifically log its use in a daily diary. At the end of two and four weeks the subjects return for testing without applying the product for at least 12 hours and they are re-evaluated under the same conditions.

Evaluation of flakiness is determined via the D-Squame Discs Method and Image Analysis. Briefly, four D-Squame discs are firmly pressed on the back of each hand with hand held uniform

pressure device and removed by gently pulling away from the skin. The D-Squame discs are mounted on clear microscope slides and labeled according to subject's name and visit. Desquamation is evaluated from the D-Squame discs via the image analyzer. Skin evaluation is carried out before treatment, and after two and four weeks of treatment.

An OPTIMA image analyzer is used to evaluate skin flakiness. The D-Squame samples containing the stratum corneocytes are placed under a camera on top of a light table and each image is imported into the image analyzer. The average Gray Value corresponding to the sample density is measured. The denser the sample, the higher the Gray Value difference. The treated skin shows a 22.5% decrease in flakiness relative to baseline after two weeks, and a 24.1% decrease after 4 weeks. The decrease in flakiness is apparently due to the observed effect on cohesion of the stratum corneum.

Example IV

This example illustrates the efficacy of the addition of cholesterol sulfate to DHA in enhancing duration of self-tanning. Two products are prepared for testing, one a control formulation containing 5% DHA, and the second the test formulation containing 5% DHA and 0.2% sodium cholesterol sulfate. A total of 10 panelists participate in the study. The control formulation is applied to the right arm and the test formulation on the other. Equal amounts of the products (800µl) are dispensed and blended in until absorbed.

Color measurements are obtained with a Chromameter before treatment, 24 hours after treatment, and 4 days and 5 days. Decrease in reflectance and increase in red coloration and yellow coloration (ΔL^*, Δa^*, Δb^*)obtained from the Chromameter are calculated as compare to baseline skin color. Total color change ΔE^* is calculated for each time point as follows:

ΔE^*= square root of $(\Delta L^*)^2+(\Delta a^*)^2+(\Delta b^*)^2$

The results, shown in Figure 2, demonstrate that there is a decrease in skin reflectance and an increase in skin redness and yellow coloration due to the self-tanning effect of the products. Total change in color values (ΔE^*) observed from the graph show that there is 10% darker color on the arms treated with the formulation containing the cholesterol sulfate as compared with the one treated with DHA alone. After 4 and 5 days, there is still 20% and 25% darker tan on the site treated with DHA and cholesterol sulfate, as compared with the site treated with DHA alone. These data show that the addition of cholesterol sulfate to DHA results in a longer lasting tan.

Example V

This example illustrates the efficacy of a composition containing DHA combined with cholesterol sulfate and a lipid mix in enhancing the intensity and duration of self-tanning. Two products are tested: a test product containing 5% DHA, 0.2% sodium cholesterol sulfate, 0.2% linoleic acid and 0.2% SC complex, containing wheat bran extract and olive oil extract, and a standard self-tanning product containing only 5% DHA as control.

A total of 22 panelists participate in the study, divided into two groups of eleven each. The control is applied on the right arm, and the test product is applied on the left arm. Equal amounts of the product (800µl) are dispensed and blended in until absorbed.

Color measurements are taken as described in Example IV. The results, shown in Figure 3, demonstrate that there is a decrease in skin reflectance and an increase in skin redness and yellow coloration due to the self-tanning effect of the products. The 5% DHA product with the lipid mix appears to retain color more efficiently during the entire seven-day study period when compared with the control product.

What is claimed is:

1. A method of retarding desquamation in the stratum corneum of the skin comprising applying to the skin a composition comprising an effective amount of cholesterol sulfate.

2. The method of claim 1 in which the composition comprises from about 0.05% to about 10% cholesterol sulfate.

3. The method of claim 1 in which the composition comprises about 1% to about 3% cholesterol sulfate.

4. A method of treating or preventing the thinning of the stratum corneum of the skin comprising applying to the skin a composition comprising an effective amount of cholesterol sulfate.

5. The method of claim 4 in which the composition comprises from about 0.05% to about 10% cholesterol sulfate.

6. The method of claim 4 in which the composition comprises about 1% to about 3% cholesterol sulfate.

7. A method of protecting the skin from the effects of UV radiation which comprises applying to the skin a composition comprising effective amount of cholesterol sulfate.

8. The method of claim 7 in which the composition comprises from about 0.05% to about 10% cholesterol sulfate.

9. The method of claim 7 in which the composition comprises about 1% to about 3% cholesterol sulfate.

10. The method of claim 7 in which cholesterol sulfate is applied in combination with at least one sunscreen.

11. A composition for protection of the skin from the effects of UV radiation comprising an effective amount of cholesterol sulfate and at least one sunscreen.

12. The composition of claim 11 in which the sunscreen is selected from the group consisting of titanium dioxide, zinc oxide, iron oxide, camphor derivatives, cinnamates, salicylates, benzophenones, triazines, PABA derivatives, diphenylacrylate derivatives, dibenzoylmethane derivatives, and combinations thereof.

13. A method for artificially tanning the skin comprising applying to the skin a composition comprising applying to the skin an effective amount of cholesterol sulfate and an effective amount of at least one self-tanning agent.

14. A composition for artificially tanning the skin comprising an effective amount of cholesterol sulfate and an effective amount of at least one self-tanning agent.

15. The composition of claim 14 which comprises DHA as the self-tanning agent.

16. The composition of claim 15, which also contains an imidazole.

17. A composition for retarding desquamation and enhancing the thickness of the stratum corneum comprising an effective amount of cholesterol sulfate and effective amounts of at least one of each of fatty acids, ceramides and a sterol.

18. The composition of claim 17 in which the fatty acid is a C_{12}-C_{20} fatty acid.

19. The composition of claim 17 in which the ceramide is ceramide III or a cerebroside.

20. The composition of claim 17 which comprises cholesterol sulfate, a C_{12}-C_{20} fatty acid, ceramide III or a cerebroside, and cholesterol.

21. A method of preventing or retarding the appearance on the skin of fine lines and wrinkles associated with aging which comprises applying to the skin an effective amount of cholesterol sulfate.

FIG. 1A

FIG. 1B

FIG. 1C

FIG. 1D

FIG. 1E

FIG. 1F

FIG. 2

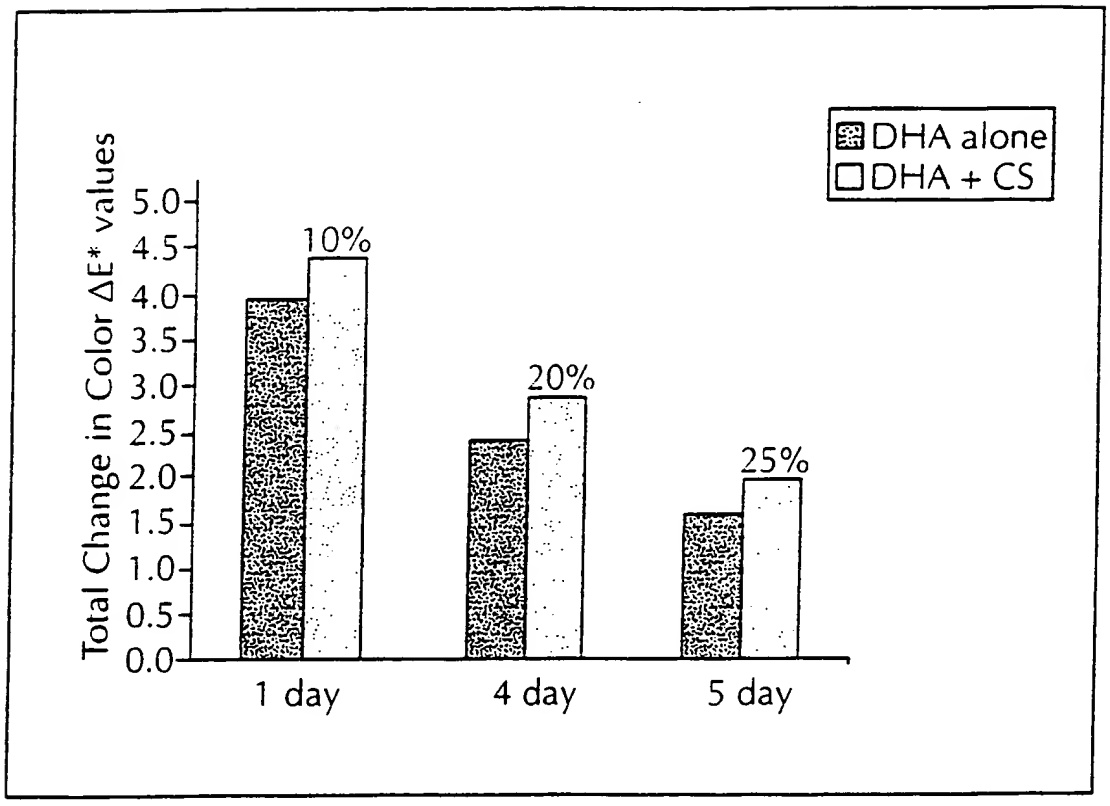
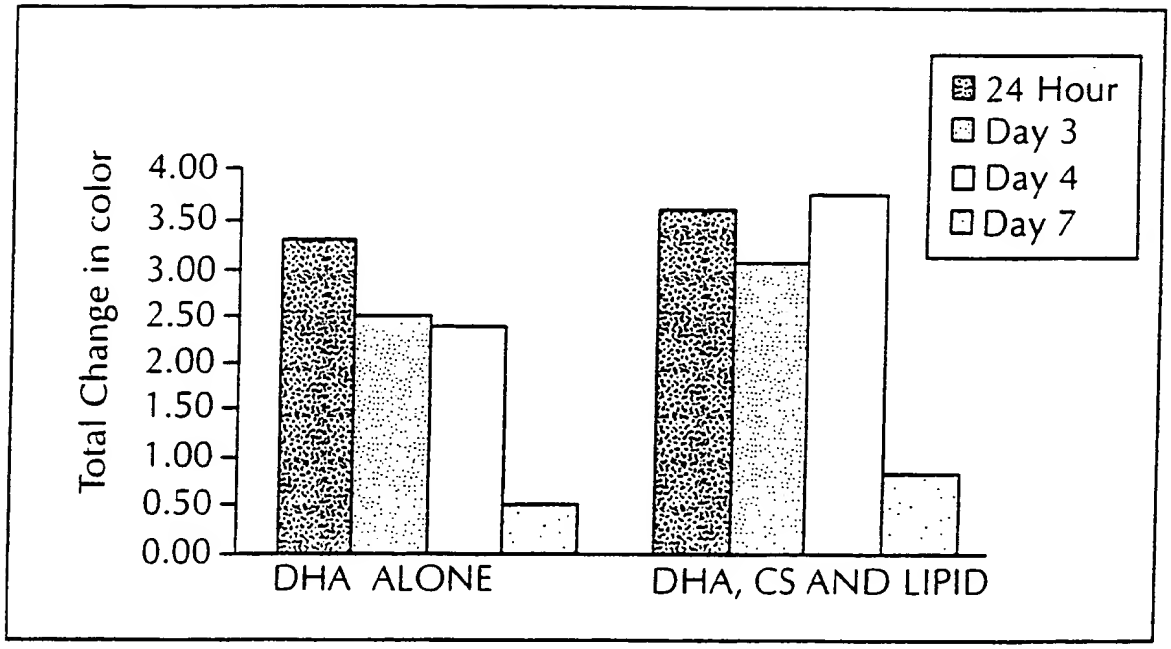

DHA alone
DHA + CS
Total Change in Color ΔE* values
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
10%
20%
25%
1 day
4 day
5 day

FIG. 3


24 Hour
Day 3
Day 4
Day 7
Total Change in color
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
DHA ALONE
DHA, CS AND LIPID

INTERNATIONAL SEARCH REPORT

Int. ..tional Application No
PCT/US 00/02750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 196 42 872 C (HENKEL KGAA) 12 February 1998 (1998-02-12) page 3, line 13 page 5, line 12 - line 23 page 5 claims ---	1-12
X	WO 90 01323 A (BERNSTEIN JOEL E) 22 February 1990 (1990-02-22) page 2, line 12 - line 23 --- -/--	1,2,5, 17,18,21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	09/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pelli Wablat, B

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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